CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-232

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug
Administration
Rockville MD 20857

NDA 21-232

1-18-02

R&R Registrations
Attention: Ronald G. Leonardi, Ph.D.
U.S. Agent for Swedish Orphan, AB
P.O. Box 262069
San Diego, California 92196-2069

Dear Dr. Leonardi:

Please refer to your new drug application (NDA) dated December 27, 1999, received December 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orfadin Capsules (nitisinone).

We acknowledge receipt of your submissions dated July 19, August 23, August 24, and November 21, 2001, and January 7, 11, and 17 (fax), 2002. Your submission of July 19, 2001, constituted a complete response to our May 3, 2001, action letter.

This new drug application provides for the use of Orfadin Capsules (nitisinone) for adjunctive therapy to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the proposed labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted January 17, 2002, immediate container and carton labels submitted January 7, 2002). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-232." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your January 7, 2002, submission to perform standard reproductive toxicity studies, as per the International Conference on Harmonisation Guidance, S5A, *Detection of Toxicity to Reproduction for Medicinal Products.*

Submission of Protocols:	By May 30, 2002
Study Start:	By September 30, 2002
Submission of Final Study Reports:	By March 30, 2003

Submit protocols and study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of the commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates and any changes in plans since the last annual report. All submissions, including supplements, relating to this postmarketing study commitment should be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

We also note that you plan to submit a prior-approval supplement for a new manufacturer of the drug substance. In your November 21, 2001, submission, you agreed to include in that supplement information on the characterization and proof of structure for the drug substance produced by the new manufacturer under the finalized manufacturing process. In addition, you agreed to submit the following information. You may address each either in the supplement that provides for a new manufacturer of the drug substance or in separate prior-approval supplements.

We encourage you to establish a voluntary registry of hereditary tyrosinemia type 1 patients treated with nitisinone to collect information on clinical outcomes with long-term use of nitisinone.

All applications for new active ingredients, new dosage form, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). You have fulfilled the pediatric study requirement at this time.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We note your launch materials submitted on August 23, 2001. At this time, please submit three copies of any additional introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Samuel Y. Wu, Pharm.D., Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

John Jenkins, M.D.
Director
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure
Package Insert (January 17, 2002)

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Jenkins
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